# 2016 Global Brain Disorders Poster Abstracts

## *Poster Abstracts*

**Principal Investigator:** Bielas, Stephanie

**Title:** Genetic Diagnosis of Neurodevelopmental Disorders with Exome Sequencing in India

**Presenters**: Anju Shukla[1], Anshika Srivastava[2], Arul M. Chinnaiyan[3], Katta M Girisha[1], Stephanie L. Bielas[2]

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The incidence of children with inherited neurodevelopmental disorders (NDD) is high in low- and middle-income countries (LMIC) and becoming an enormous burden on health care resources. While individual inherited NDD are rare, in aggregate they affect millions of people. Whole exome sequencing (WES) has risen to the forefront of genetic testing in High and Middle Income Countries (HMIC) based on its potential to uncover genetic causes responsible for inherited NDD conditions, while circumventing bottlenecks caused by candidate gene screening approaches. An ongoing collaboration between University of Michigan Medical School, USA and Kasturba Medical College at Manipal University, India is establishing infrastructure to use WES for genetic diagnosis of NDD in the Department of Medical Genetics at Manipal University. To address common hurdles in adopting this technology we (1) have identified reliable and timely sequencing options, (2) continue to build WES bioinformatic analysis capabilities, and (3) are supplementing education of medical genetics and genetic counseling professionals. Through these efforts we have performed trio-WES on 10 families, identifying 5 novel alleles for known genetic causes of NDDs. No pathogenic variants were identified in 5 probands. The diagnostic success with this small sample size is on par with that for clinical WES in HMIC. We look forward to building on every aspect of this experience. Our newly established bioinformatics infrastructure will allow WES data to be periodically reanalyzed in light of new genetic findings, allowing us to improve the rate of genetic diagnostic over time. This data will also benefit genetic diagnosis of inherited diseases and genetic testing policy in India nationally.

**Principal Investigator:** Boivin, Michael

**Title: Automated eye tracking technology improves the sensitivity of an early childhood vigilance test (ECVT) of attention in Ugandan children perinatally exposed to HIV**

**Presenters:** Weiss, Jonathan[1]; Chhaya, Ronak[1]; Seffren, Victoria[2]; Sikorskii, Alla[3]; Familiar, Itziar[4]; Ruiseñor-Escudero, Horacio[4]; Nakasujja, Noelene[5]; Giordani, Bruno[7]; Boivin, Michael J.[6,7]

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**Objectives:** We evaluated the use of automated eye tracking technology to enhance the sensitivity of the Early Childhood Vigilance Test (ECVT) of attention with younger children perinatally exposed to HIV in rural Uganda. We also evaluated whether this technology could enable the ECVT to correlate better with a color-object association test

(COAT) of memory and learning and the Mullen Scales of Early Learning (MSEL).

**Participants and Methods:** 44 children were evaluated with the ECVT, COAT, and MSEL (24 boys M=52.3 SD=11.4 months of age; 20 girls M=52.4, SD=12.2). The ECVT measures the proportion of time a child looks at the monitor during a cartoon video. The ECVT is typically scored from a webcam using PROCODER software. We also programmed a Tobii X2-30 portable camera to record the child's pupil direction during the cartoon to calculate % time watching.

**Results:** Children watched 78% of the cartoon using Tobii automated eye tracking, while PROCODER webcam scoring resulted in an average of 67% ($r$=0.84, $P$<0.001). Older children performed better on the ECVT ($r$=0.41, $P$=0.008), although no gender differences were observed. ECVT Tobii eye tracking significantly correlated with COAT immediate recall for color-object placement

associations (tracking moving animals $r$=0.33, $P$=0.019; total percent time screen gaze $r$=0.31, $P$=0.035), and with MSEL Fine Motor performance (visual-spatial learning with motor response; $r$=0.33, $P$=0.037). ECVT webcam PROCODER % was also significantly correlated with COAT memory ($r$=0.42, $P$=0.005) and learning (r=0.38, $P$=0.011), but not with MSEL Fine Motor.

**Conclusions:** Enhancing the sensitivity of the ECVT by using automated eye tracking technology improves the extent to which it correlates with other visual-spatial measures of working memory and learning in Ugandan children perinatally exposed to HIV. These findings imply that eye tracking technology has the potential of improving the validity and reliability of other neurocognitive measures in children at-risk in low-resource settings.

**Principal Investigator:** Boivin, Michael

**Title:** The use of eye-tracking technology in a modified Fagan test to assess neurocognitive development in rural Ugandan infants exposed to HIV

Chhaya, Ronak[1]; Weiss, Jonathan[1]; Seffren, Victoria[2]; Sikorskii, Alla[3]; Familiar, Itziar[4]; Ruisenor, Horacio[4]; Nakasujja, Noeline[5]; Giordani, Bruno[6]; Boivin, Michael[4,7,6]

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**Purpose:** The Fagan test of infant intelligence uses gaze length for familiar and unfamiliar human faces to gauge working memory in infants. We modified the Fagan test for use with an automated eye-tracking instrument to measure infant gaze length favoring unfamiliar compared to familiar faces in Ugandan children born to mothers with HIV.

**Method:** A modified Fagan test was administered to 31 non-infected Ugandan infants perinatally exposed to HIV, 6 to 12 months of age (11 boys; $M$=0.69 yrs, SD=0.14; 20 girls; $M$=0.79, SD=0.15). A series of faces are presented in a repeated pattern for a fixed presentation length throughout a six-minute video (unknown Face 1 is presented for 25 seconds, followed by 15 seconds where the now familiar Face 1 is presented with unfamiliar Face 2). We programmed a Tobii X2-30 infrared camera for pupil direction for an automated eye-tracking measure of gaze location and length in response to digitized photographs of local Ugandan faces selected to correspond to the gender, age (adult, child), face expression, and orientation of the original series of Fagan test faces. We correlated modified Fagan test performance to performance on the Mullen Scales of Early Learning (MSEL), which is easier to administer in low

resource settings and provides a composite measure of fluid intelligence thought to underlie cognitive ability development in children 0 to 68 months of age.

**Results:** As anticipated, infants spent significantly more time gazing at the novel picture than familiar over 10 novelty preference trials ($t$=9.17, $P$<0.001). Boys tended to look at the faces longer than girls ($t$=1.98, $P$=0.06). The MSEL was correlated with overall time spent looking at the video ($r$=0.52, $P$=0.004). The MSEL Fine Motor scale, which measures visuospatial working memory requiring a motor response, was correlated with gaze length at novel faces ($r$=0.40, $P$=0.03), gaze length at familiar faces ($r$=0.38, $P$=0.04), and overall gaze length during the video ($r$=0.54, $P$=0.002).

**Conclusion:** Our modified Fagan test resulted in a sensitive working memory measure predictive of overall child development. Use of eye scanning technologies in infants can provide a neurocognitive outcome for evaluating risk and resilience in low-resource settings for at-risk children.

**Principal Investigator:** Carabin, Hélène

**Project Title:** EFECAB: Improving pig management to prevent epilepsy in Burkina Faso

**Presenter:** Carabin, Hélène

This study aims to compare epilepsy and Severe Chronic Heachaches village-level prevalence estimates with and without the inclusion of sampling probability-weights in the analysis. Baseline data from a community-based randomized trial conducted in 60 villages located in three provinces of Burkina Faso between February 2011and January 2012 were used. Thirty out of 31 departments were selected and two villages in each department were randomly selected. In each village, a stratified random sampling approach was used to select 80 concessions based on the presence of sows and piglets. One household per concession and one individual per household were randomly selected, which resulted in 4,795 study participants (and households). Participants were interviewed with a screening questionnaire for epilepsy and SCH. Screened positive participants were later confirmed

**Principal Investigator**: Grigorenko, Elena

**Title:** A Community-Based Evaluation of Interventions for Orphans and Vulnerable Children (OVC) Affected by HIV/AIDS

**Poster Author:** Tan, Mei

While the prevalence of HIV/AIDS, its transmission rate, and other effects of this condition on health have been monitored, little is known in Zambia about the developmental milestones, life conditions, outcomes and the support systems for orphans and vulnerable children affected by HIV/AIDS (HIV-OVC). To undertake such a study, we first had to decide how to identify the appropriate sample of children via an apt definition of HIV-OVC, to be applied in the region to be studied—rural Southern Province, Zambia.

After consideration of the recently expanded and increasingly multi-faceted definitions of OVC living in the context of HIV/AIDS, we decided in the end to use a very basic definition, based simply on orphanhood, the child's health status, and the health status of the relevant adults in the child's life (caregivers and parents). We applied this definition using the basic structure and content of a screener originally developed by UNICEF in 2005, the OVC module of the Multiple Indicators Cluster Survey, 3rd version, the MICS3. We then adapted the MICS3 to work within the cultural context of our study area.In this poster, we discuss why we chose the MICS3, how we adapted it, then share some of our initial findings about family structure and the prevalence of children affected by HIV/AIDS in this rural community. Beyond its relevance to our own study, the information gleaned here may suggest new questions or new avenues for follow-up concerning the changing conditions for HIV-OVC in Zambia as their health and family environments evolve with advancements in medical care and new social/career opportunities for young people.

**Principal Investigator:** Harder, Valerie

**Title:** Motivational Interviewing Treatment for Alcohol Abuse in Kenya

**Poster Presenters**: Valerie Harder, Victoria Mutiso, David Ndetei

**Background**: Mental disorders, such as alcohol abuse and psychiatric problems, are highly prevalent among impoverished Kenyans, are associated with HIV/AIDS, and the absence of evidence-based treatment for mental disorders in rural Kenya makes this a major public health concern in need of innovative solutions. In this R21 research project, our main objective is to develop and test the feasibility and efficacy of a mobile phone-based motivational interviewing (MI) intervention for alcohol abuse, provided by Kenyan clinicians, as an innovative approach to treating mental disorders among impoverished Kenyans.

**Methods:** Adults being tested for or seeking treatment for HIV/AIDS were recruited from a rural primary care health clinic in Kenya, screened using the Alcohol Use Disorders Identification Test (AUDIT), and selected (N=322) for the study if alcohol abuse was detected. Subjects were randomized into waitlist for one month, immediate mobile MI, or immediate standard in-person MI. One session of MI lasting 30 minutes on average was provided to all subjects, and re-assessment using the first three questions of the AUDIT (AUDIT-C; ranging between 0-12) was conducted over the mobile phone at one month and six months. Waitlist subjects received an additional reassessment at 1 month before receiving MI. Three Kenyan clinicians, a medical doctor, a masters-level clinical psychologist, and a bachelors-level nurse were trained in MI, and each treated approximately one third of the subjects.

**Results**: For waitlist (N=76), baseline and one month reassessment AUDIT-C scores did not differ (baseline mean=7.5, reassessment mean=6.4). For all subjects there was a significant decrease in the AUDIT-C score from baseline to reassessment (N=201) at one month (baseline mean = 7.8, reassessment mean = 3.2) and from baseline to reassessment (N=184) at six months (reassessment mean = 1.8). Results did not differ by randomization arm; we found no differences in the response to

treatment in-person compared to mobile phone.

**Discussion:** Overall, our study found MI to be a feasible and efficacious intervention for alcohol abuse in this adult sample in Kenya. Waitlist subjects did not decrease alcohol use just because they were being assessed by our clinicians, and we found no difference between in-person MI and MI conducted entirely over the mobile phone. A major limitation of this study is that over 100 subjects were lost to follow up before receiving a reassessment at 1 month and an additional 20 were lost to follow up before receiving reassessment at 6 months. Our results suggest that trained clinicians can provide effective treatment for alcohol abuse over the mobile phone for hard to reach rural alcohol abusing adults in Kenya without ever meeting them in person, and our results suggest that one session of MI may be adequate. Further studies are necessary in a larger sample, with longer follow-up time, compared against other treatment modalities, and to treat co-occurring psychiatric disorders.

**Principal Investigator:** Adnan Hyder

**Title:** Developing an internet-based traumatic brain injury registry in Uganda: A review of published literature

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**Background:** Worldwide, over 10 million people suffer Traumatic Brain Injury (TBI). Data on the burden of injuries and TBI in Uganda are scarce, which has prevented the magnitude of the burden to be appreciated and has posed a barrier to defining risks, vulnerable groups, and the impact of potential interventions. The primary aim of this review was to define core variables for an internet-based data registry focused on TBI in Uganda.

**Methods**: A comprehensive review was conducted. Six databases including PubMed/Medline, Embase, Scopus, Cochrane Reviews, System for Information on Grey Literature and Global Health Ovid were searched for literature pertaining to TBI in the African region and TBI registries in low- and middle-income countries. A spreadsheet was used to extract core variables and definition used for TBI.

**Results:** Thirty-five articles were identified as relevant to the focus of inquiry. The majority of the articles were from Nigeria, followed by South Africa and Tunisia. Few included definition used to define TBI. The most commonly collected core variables were demographics, injury event, initial assessment, emergency department care, in-patient care and outcome at hospital discharge.

**Conclusion:** Registries are critical for quantifying injury burden and improving quality of care. This study unveils the key variables for TBI registries in LMICs. It also highlights the need for more studies to be conducted on this important public health issue.

**Principal Investigator:** Chandy John

**Presentation Title:**
Neurodevelopmental outcomes in severe malaria

**Presenter:** Dr. Robert Opoka co-investigator
Authors: **Opoka R**, Idro R**,** Bangirana P, Namazzi R, Cusick S, Georgieff M, Datta D, Postels D, Vercellotti G, John CC

**Background:** Children who survive cerebral malaria (CM) are at risk of developing neurodevelopmental impairments (NDI) after the CM episode. We previously showed that severe malaria anemia (SMA) was also associated with cognitive impairment similar to impairment following CM. The goal of the grant is to investigate whether survivors of the major forms of severe malaria treated with artesunate have associated risk of developing NDI. Specifically we aim to establish the functional areas, degree and immunological, metabolic and nutritional risk factors associated with NDI.

**Project methods :** To recruit a cohort of 720 children aged 6 to 48 who present with any of the 5

common manifestations of severe malaria (SM) or are healthy community children (CC) from the families or neighborhoods of the children with SM. Enrolled children are followed up for 12 months. During hospitalization (SMs) or at enrolment (CCs) blood samples are taken for immunological, metabolic and micronutrient testing. Cognitive and behavioral assessments are done 12 months after enrollment using a battery of tools validated for use in African settings. Immunological, metabolic and micronutrient risk factors in children with SM will be compared to neurodevelopmental outcomes, including cognition, attention and behavior.

**Progress to date:** The study is currently enrolling children in 2 hospitals in Uganda. As of February 22, 2016, 443 children have been enrolled. The forms of severe malaria affecting the enrolled children include CM (n=47), SMA (n=114), respiratory distress (n=62), malaria with repeated seizures (n=106), and prostration (n=36). We have also enrolled 78 CC. To date, 102 children have completed the study, and 47 are no longer active in the study due to death, withdrawal of consent, or loss to follow up.

**Challenges:** The biggest challenge arose from the 17% funding cut at the start of the study. The acute budget problems were compounded by the need to have a second study site due to the changing burden of inpatient malaria. Supplemental university funding has been critical to allowing the study to continue and to achieving study goals. In addition, the study has been supported though use of infrastructure developed through previous grant funding and university funding, incorporation of personnel with high levels of training from the previous grant into the current study, leverage of capacity building from our D43 training grant, and a strong study team work ethic.

**Conclusions and future plans:** The NDI study is enrolling and on course to be completed in time. We plan to begin initial lab testing later this year, and continue testing on samples from the prior study and analysis of data from the prior study.

**Principal Investigator:** Johnson, David Kevin

**Title:** Fitness Predicts Cognitive Performance in Urban Latin Americans

Monica Salazar-Villanea[1], Jose Moncada-Jimenez[2], Mauricio Garnier-Villareal[3], Edward Liebmann[3], Esteban Montenegro-Montenegro[1], Eric D. Vidoni[4], and David K. Johnson[3&4]

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2. University of Costa Rica, Research Center for Human Movement Sciences

3. University of Kansas, Department of Psychology

4. University of Kansas, Alzheimer's Disease Core Center

**Introduction:** Our group recently conducted a randomized clinical trial in US dwelling older adults that indicated increasing cardiorespiratory fitness (measured by VO2 peak on treadmill) resulted in better visuospatial cognition in active healthy older adults. Maximizing an individual's cardiorespiratory fitness was the most important therapeutic target for achieving cognitive benefit. The Epidemiology and Development of Alzheimer's Disease (EDAD; R21TW009665) examined the role of fitness on cognitive performance in urban dwelling Costa Rican's.

**Methods:** We applied standard cognitive and physical fitness assessment batteries to a large sample of urban dwelling Latino volunteers at our University of Costa Rica sponsored satellite clinic in San Jose. The battery was a comprehensive and empirically rigorous assessment of the environmental versus organismic determinants of healthy aging and dementia in Latin Americans. Cognitive outcomes reported here were latent residual scores derived from a battery of 12 common neuropsychological tests: Verbal Memory, Visuospatial Processing, and Simple Attention. Other outcome measures were the 6-minute walk, a proxy of cardiorespiratory fitness and measures of function and disability.

**Results:** Higher cardiorespiratory fitness was significantly correlated to Simple Attention and Visuospatial Processing abilities, replicating previous published work.

**Conclusion:** Low and middle income nations will experience an unprecedented growth of the elderly population and subsequent increase in age-related neurological disorders that requires effective strategies for promoting healthy brain aging and the prevention of Alzheimer's disease. Alzheimer's disease destroys the active, productive lives of its victims and devastates their families financially and emotionally. It is estimated to affect millions of older people throughout the world. Aerobic training for older Latinos was safe and effective. Cardiorespiratory fitness (VO2peak) and visuospatial cognition are a clinically meaningful therapeutic targets for future prevention trials in Latin America.

**Principal Investigator:** Vishwajit L Nimgaonkar MD, PhD (USA), Hader Mansour MD, PhD (Egypt)

**Title:** Multi-pronged genetic studies of schizophrenia in an inbred population

**Presenter:** Hader Mansour MD, PhD (Egypt)

**SPECIFIC AIMS:**

Aim 1. Homozygosity by descent (HBD) analysis to identify schizophrenia risk polymorphisms

Aim 2. Follow up sequencing and bioinformatics analysis

Aim 3. Phenotypic expression of identified SZ risk variants among multi-generational families

Aim 4. Continue sustainable research infrastructure and capacity building:

**STUDIES AND RESULTS**

Research Following approval from MU and the University of Pittsburgh Ethics Committees, we have recruited more than 500 participants (cases, controls and parents). We have completed HBD analysis on 249 cases and 284 controls using genome wide panel of SNPs. Six suggestive HBD regions were identified. Exome sequencing was completed on cases HBD for each region (N= 3 cases/region). We are presently evaluating these data in relation to published data in other ethnic groups. Our plans are as follows: (i) sequence other individuals HBD at each region for selected mutations; (ii) genotype the remainder of the sample and conduct HBD analysis, (iii) evaluate data in relation to a similar sample collected in Pakistan by Dr Muhammad Ayub, Queens University Kingston, Canada.

Infrastructure building We are holding regular internet training sessions in bioinformatics and genetic analysis techniques for our overseas collaborators. Additional training was held in 2014 and 2015 at the University of Pittsburgh for four colleagues specializing in bioinformatics, data management and analysis, as well as molecular genetic techniques. We have already purchased dedicated computer equipment, a freezer and a qPCR machine and installed them in a genetics lab at Mansoura, Egypt that we helped establish. Our collaborators in Egypt scheduled a public symposium in Cairo, Egypt on September 9-11, 2015. The PIs participated in the symposium, provided research mentorship and updated the audience about the progress of our training and research. Our training work is coordinated with a separate training grant from NIH (1 D43 TW009114-01, 08/2014-07/2019).

**Principal Investigator:**
Radulovic, Jelena

**Title:** Pre-Clinical and Patient Studies of Affective Disorders in Serbia

**Poster author:** Jelena Radulovic

Rooted in recent wars, displacement, and socio-economic instability, Serbia has established a 13.5% increase in the prevalence of post-traumatic stress disorder (PTSD) and major depression, making them the second largest public health problem in this LMIC country. In parallel, the health system has deteriorated, facing multiple challenges in areas of basic and clinical research. We developed a collaborative program between Northwestern University (USA) and Vinca Institute (Serbia) in basic and translational research relevant for major affective disorders. We initiated an investigation of molecular endophenotypes of PTSD and depression by focusing on a newly

proposed interaction between glutamatergic and glucocorticoid signaling, and identified the phosphorylation state of gluccocorticoid receptor as a powerful predictor and useful biomarker for stress-associated depressive episodes.

**Principal Investigator:** Rascovsky, Katya

**Title: Young Onset Dementia in Colombia**

**Presenter:** Katya Rascovsky

Young-onset neurodegenerative diseases such as frontotemporal degeneration (FTD) and early-onset Alzheimer's Disease (AD) affect individuals in their most productive years and represent a major source of disability. As disease-modifying clinical treatment trials emerge for specific pathologies, it will be necessary to 1) improve differential diagnosis of young-onset dementias, 2) develop sensitive and specific clinical, imaging and biofluid biomarkers that can be collected easily and reliably in developed and developing countries, 3) establish patient registries to facilitate multi-center research and recruitment in clinical trials. In collaboration with our colleagues at the Penn Frontotemporal Degeneration Center (PFTDC) and the Center for Neurodegenerative Disease Research (CNDR), we are working to establish sustainable clinical research collaborations between the University of Pennsylvania and several dementia centers in Latin America. Currently, we have ongoing projects with the following centers: 1) Memory Clinic and Institute on Aging, Pontificia Universidad Javeriana (MCIA) in Bogota, Colombia, 2) Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez" (INNN) in Mexico City, Mexico, 3) Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI) in Buenos Aires, Argentina 4) Sanatorio de los Arcos in Buenos Aires, Argentina and 5) the Peru Young-Onset Dementia Network (PYN), a consortium of researchers at the Universidad Peruana Cayetano Heredia (UPCH), Clínica Internacional and DPI Imaging Center in Lima, Peru. We are building research capacity at these sites by developing and implementing standardized methods of clinical assessment, imaging and genetics, as well as data handling, analysis and transfer. This partnership aims to create the critical infrastructure necessary for a Latin American Registry for Dementia which will facilitate collaborations between Latino dementia centers in the US and abroad. It will also help elucidate biological and cultural differences in the diagnosis and management of young-onset dementias in Latin America.

**Principal Investigator:** Ringman, John

**Title:** Attitudes and Knowledge of Clinical Trials to Prevent Autosomal Dominant Alzheimer Disease in Mexico and the U.S.

**Presenters: John M. Ringman, M.D.**1, Maria Casado, B.A.2, Yaneth Rodriguez Agudelo, Ph.D.3, Esmeralda Matute, Ph.D.4 and

Mellissa Withers, Ph.D.1, (1)Keck School of Medicine at USC, Los Angeles, CA, USA, (2)Easton Center for

Alzheimer's Disease Research at UCLA, Los Angeles, CA, USA, (3)Instituto Nacional de Neurologia y Neurocirugia,

Distrito Federal, Mexico, (4)University of Guadalajara, Guadalajara, Mexico

**Abstract Text:**

**Background:** Persons at-risk for autosomal dominant Alzheimer's disease (ADAD) provide an opportunity to prevent disease by intervening years before symptom onset. Trials of pharmacological interventions in this context are challenging as potential subjects are faced with complex issues when deciding to participate. Such issues are difficult for highly educated persons in industrialized countries and even more challenging for persons not familiar with such matters. We sought to assess attitudes about research and knowledge of ADAD in persons from such families in both rural and urban settings.

**Methods:** 50 persons from families harboring ADAD mutations residing in Mexico (n=39) or the U.S. (n=11) completed the Research Attitudes Questionnaire (RAQ) and a

Familial Alzheimer's Disease Genetics Questionnaire (FADGQ). They then heard a presentation on AD, ADAD, and clinical trials and were given the opportunity to ask questions. A subset of subjects (n=44) then completed the questionnaires again. RAQ scores (-14 to + 14, higher scores representing a more positive attitude towards clinical research) and FADGQ scores (0 - 9, higher scores representing more understanding of ADAD genetics) were compared between subjects living in urban (n=22) vs. rural (n=28) settings by t-tests and scores before and after the presentation were compared by paired t-tests, both in the total population and divided by urban vs. rural residence.

**Results:** At baseline there were no differences between urban and rural inhabitants in their attitudes regarding research but persons living in urban settings scored higher on the FADGQ(6.2 vs. 5.3, $p = 0.02$). Though mean scores on the RAQ (6.4 to 7.4) and FADGQ (5.6 to 5.9) were moved in the direction favoring clinical research and knowledge regarding ADAD, the changes were not significant. When the groups were divided by urban vs. rural settings, there was a greater impact on research attitudes in urban dwellers (5.9 to 7.8, $p = 0.14$) and a greater impact on ADAD knowledge in rural inhabitants (5.3 to 5.8, $p =0.053$).

**Conclusions:** It is essential to educate potential ADAD prevention trial subjects but it requires intense and repetitive interactions with families. Urban residents may benefit more from education regarding trial methodology and some rural inhabitants from a better understanding of the disease

**Principal Investigator:** Rohlman, Diane

**Project title:** Building Capacity Through Research

Ahmed Ismail[1, 2], Gaafar Abdel Rasoul[2], Olfat Hendy[2], James R. Olson[3], Matthew R. Bonner[3], Diane S. Rohlman[1]

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Subtle changes in health outcomes due to pesticide exposures result in large social and economic consequences. Universities in Egypt do not have resources, training, or experience to carry out comprehensive exposure assessments or to effectively evaluate health effects associated with pesticide exposure. Therefore, it is important to build capacity among Egyptian researchers to make them competitive at the international level for carrying out research addressing public health concerns. As part of an R01 project funded by the Fogarty Institute and the National Institute of Environmental Health Sciences (ES022163), a range of activities designed to build and expand research capacity among faculty and students at Menoufia University are underway. Videoconferences are used to allow researchers from the US to meet with faculty and students from Menoufia University. A competitive pilot grant program introduced this year will fund projects from researchers at Menoufia University and the National Liver Institute. To date, sixteen letters of intent to submit were received. Applications will be scored using NIH criteria and feedback provided to the investigators. The pilot grant program will provide researchers with the opportunity to collect preliminary data which will increase their competitiveness to apply for additional funding. Research skills addressing various topics (e.g., questionnaire development, exposure assessment) are discussed during the annual team meeting and team members have the opportunity for additional training in US laboratories. Finally, a project webpage was developed as a resource for team members and other faculty and students. This site contains project related information, guidelines and resources for the pilot grant program, and links to project publications. These activities have expanded the capabilities of team members and other faculty and students at Menoufia University.

**Principal Investigator:** Sacktor, Ned

**Title:** Peripheral Neuropathy is Common and Associated with Functional Impairment in HIV+ and HIV- Individuals in Rural Uganda

Deanna Saylor[1], Gertrude Nakigozi[2], Noeline Nakasujja[3], Xiangrong Kong[4], Kevin Robertson[5], Ronald H. Gray[4], Maria J. Wawer[4], Ned Sacktor[1]

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**Objective:**
To determine the prevalence, risk factors and functional impact of peripheral neuropathy (PN) in a cohort of adults in rural Uganda.

**Background:**
PN is a common and potentially debilitating neurologic complication of many conditions, including HIV infection, diabetes, and nutritional deficiencies. Systematic studies of PN in sub-Saharan Africa are lacking.

**Design/Methods:**
Participants in the Rakai Community Cohort Study underwent detailed neurological evaluations including assessment of subjective PN symptoms, functional measures (Patient Assessment of Own Functioning Inventory (PAOFI) and Karnofsky scores), and neurological examination by a trained medical officer. PN was defined as $\geq$ 1 subjective symptom and $\geq$ 1 sign of PN on examination. PN risk factors and functional status differences were determined using t-tests for continuous variables and chi-squared tests for categorical variables.

**Results:**
538 participants were enrolled: mean age=35 years, 51% male, 57% HIV+ (200 with CD4 count 350-500; 107 with CD4 count < 200). PN was more prevalent among HIV+ than HIV- participants (24% vs. 8%, p<0.001). Among HIV+ participants, those with PN were older (38 vs. 35 years, p=0.01), more likely to have CD4 counts < 200 compared to CD4 350-500 (44% vs. 32%, p=0.05), reported more fatigue (30% vs. 15%, p=0.01), and had lower functional performance measured by PAOFI (142 vs. 149, p=0.006) and Karnofsky (89 vs. 93, p<0.001) scores than those without PN. Among HIV- participants, those with PN were more likely to have diabetes (6% vs. 0.4%, p=0.02) and lower Karnofsky scores (92 vs. 95, p=0.03) and showed a trend toward older age (38 vs. 34 years, p=0.09), higher isoniazid use (11% vs. 3%, p=0.06), and more fatigue (11% vs. 7%, p=0.08).

**Conclusions:**
PN is common in rural Uganda and associated with functional impairment especially among HIV+ adults. Further work is needed to improve diagnosis and management of PN in resource-limited settings.

**Principal Investigator:**
Sajatovic,Martha;
Katabira, Elly

**Title:** Reducing Stroke Burden in Uganda

**Abstract:**
Stroke is a neurological condition with rapidly increasing burden in many low- and middle income countries. Africa is particularly hard-hit due to rapid population growth, patterns of industrialization, adoption of harmful western diets, and increased prevalence of risk factors such as hypertension and obesity. However, early identification and management can reduce burden. Investigators from Makerere University in Kampala, Uganda and from Case Western Reserve University, Ohio, U.S.A. are conducting a 3-phase project consisting of; 1.) A mixed-methods assessment of barriers and facilitators to stroke risk reduction in Uganda; 2) Development of a self-management approach (SMA) to reduce stroke risk in Ugandans, and 3.) Establish a clinical trial infrastructure and data procedures preparatory to implementation of a risk reduction trial. In Phase 1 the investigators are conducting an epidemiological survey in 440 individuals to better understand stroke knowledge and attitudes. A sub-sample qualitative assessment is being conducted using individual and group-format methodologies. Survey and qualitative data will be presented. Phase 2 will adapt a successful SMA initially developed for African-Americans. In Phase 3, appropriate measures will be selected, staff will be trained in measure implementation, and the SMA will be finalized for delivery using nurses and Peer Dyads (individuals who have had success in managing stroke risk factors). Finally, in a proof-of-concept exercise, the nurses and Peer Dyads will conduct the SMA with the 2 SMA targets (one group of individuals at risk for stroke and one group of individuals who have had stroke).

**Principal Investigator:** Shin, Jin

**Title:** The Effects of a home-based intervention conducted by college students for young children with intellectual delays in Vietnam

**Abstract:**

The purpose of the project was to assess the efficacy of a home-based intervention program for young children (n= 64, ages ranging from 3-6 years) with developmental delays in Vietnam. Assessment of the program efficacy was carried out by comparing children who received services for 6 months and those who did not. It was hypothesized that the children in the intervention would show greater progress in adaptive behavior than the children in the control group. Participants were children recognized as having developmental delays by teachers in kindergarten programs, confirmed as developmentally delayed by trained evaluators based on the Vineland Adaptive Behavior Scale-II (VABS-II), then randomly assigned to intervention and control groups. Twenty student teachers who were studying psychology and education were recruited from a teaching university in Hanoi and were provided with pre-program training and ongoing supervision by special education specialists. The outcomes of the program were examined at 0, 3, and 6 months using the VABS-II. The intervention group improved significantly more than the control group in overall adaptive functioning ($F = 5.0$, $p < .01$) and in the areas of communication ($F = 2.8$, $p < .05$), social skills ($F = 2.7$, $p < .05$) and motor skills ($F=7.6$, $p < .001$). The results demonstrate the feasibility of carrying out the intervention program using teachers with no prior experience of working with children with delays/disabilities, which can be important in countries such as Vietnam, where professional resources are scarce for working with this special population.

**Principal Investigator:** Shoptaw, Steven

**Title:** Combating craving with contingency management: neuroplasticity and methamphetamine abuse in South Africa

**Presenter:** Brooks, Samantha

Psychological intervention with working memory training increases basal ganglia volume: A VBM study of inpatient treatment for methamphetamine dependence

Protracted methamphetamine (MA) use is associated with decreased control over drug craving and reduced brain volume in the frontostriatal network. However, the nature of volumetric changes following a course of psychological intervention for MA dependence is not yet known. Methods: 66 males (41 MA patients, 25 healthy controls, HC) between the ages of 18-50 were recruited, the MA patients from an in-patient drug rehabilitation centre and the HC via public advertisement in Cape Town, South Africa. 17 MA patients received 4 weeks of treatment as usual (TAU), and 24 MA patients completed TAU plus daily 30 minute cognitive training (CT) using an N-back working memory (WM) task. Magnetic Resonance Imaging (MRI) at baseline and 4-week follow-up were acquired and Voxel-based morphometry (VBM) was used for analysis. Results: TAU was associated with increased bilateral striatum (caudate/putamen) volume, whereas CT was associated with more widespread increases in volume incorporating other areas of the basal ganglia with reduced bilateral cerebellum volume, coinciding with improvements in impulsivity scores. Conclusions: While standard psychological intervention is associated with increased volume in mesolimbic regions, the utilisation of novel interventions that boost neural plasticity such as WM training, or contingency management may be the way forward for substance use disorders.

**Project title:** Chemokines in Cerebral malaria in Zambian Children

**Presenters:** James Chipeta*, Agnes Mtaja*, Evans Mulendele*, Daniel Mwimbe*, Carlos Pardo-Villamizar** and Monique Stins**#.

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Cerebral malaria (CM) is a clinical syndrome associated with *Plasmodium falciparum* infection that is associated with a high

mortality of up to 30%,particular in children. Neurological symptoms and signs include impaired consciousness, coma, delirium, seizures, and increased intracranial hypertension. It has recently become apparent that in African children, persistent neurologic deficits, including recurrent seizures and learning disabilities occur after survival of CM episodes.

Central to *P. falciparum* pathophysiology is sequestration of trophozoite and schizont stages of *P. falciparum*-infected red blood cells (PRBC) to the brain blood vessel endothelium. *Plasmodium* differs from other neuropathogens that invade the brain as PRBC do NOT cross the blood-brain barrier (BBB) into the central nervous system, but are still able to elicit neuronal dysfunction, as observed in P. *falciparum* CM.

Since the BBB endothelium is located at the interface of PRBC and the brain, we hypothesize that activation of BBB endothelium plays a role in conferring neurological dysfunction. The BBB endothelium responds to PRBC's with increased transcription and release of large amounts of cyto-and chemokines. These inflammatory molecules released to the brain side may contribute significantly to the observed neurological dysfunction in CM.

To verify and validate our *in vitro* findings for the human situation and to explore potential future adjunctive therapies we set up a collaboration with University Teaching Hospital, Lusaka, Zambia with the aid of an R21 research and capacity building funding from the NIH Fogarty Program "Brain Disorders in the Developing World: Research across the lifespan".

As outlined in our R21 proposal we have set a solid basis for an extended future collaborations, have initiated collection and analysis of blood and CSF samples of a limited patient group. Logistical and teaching support for Zambian investigators was provided via means of hosting the laboratory scientist Mr Mwimbe in our laboratories at Johns Hopkins, Baltimore and by visiting UTH for teaching purposes.

We intend to continue our collaboration and research that will focus on the role of chemokines in CM-mediated neurological dysfunction, how this affects a patient's life and development, and how the neurologic sequelae in CM patients can be prevented.

**Principal Investigator: Tshala-Katumbay, Desire**

**Title:** Transgenerational risks of epilepsy in a nutritionally challenged and onchocerciasis endemic area of the Democratic Republic of Congo (DRC): preliminary results

**Presenters:**

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**Introduction**

Epilepsy with neurodevelopmental delays are increasingly reported in Sub-Saharan Africa. Of particular interest and complex pathogenesis are the epileptic syndromes prevalent in onchocerciasis-affected areas of Tanzania, Southern Sudan, Northern Uganda and, reportedly, Northern Democratic Republic of Congo (DRC). The epidemiology of these newly described syndromes remains unclear in spite of the high cost burden to local populations, particularly, children and

adolescent who appear to be more vulnerable, stigmatized, and more likely to drop out of schools. Possible mechanisms include but not limited to *onchocerca volvulus* (OV) infection, nutritional challenges, and/or genetic polymorphisms.The aim of this study was to characterize the dietary patterns and nutritional status of onchocerciasis affected populations reportedly prone to high prevalence of epilepsy in the DRC.

**Methods**

A cross-sectional study surveyed a sample of 27 randomly selected villages comprising 400 households within the surroundings of the Kasangulu health district in the Bas-Congo province of the DRC, September 2014.Nutritional endpoints were assessed using SMART (Standardized Monitoring and Assessment of Relief and Transitions) and ENA software (2013 version).Interviews and focus group discussions, as well as anthropometric measurements (age-for-height Index, weight-for-age index, and BMI) on558 children (aged 5-18 years), were carried out by an expert team from PRONANUT (Program National de Nutrition), Ministry of Health, DRC.A team of trained physicians had face-to-face interviews with 84 epileptic consenting subjects (aged 8 - 51 years)and their close relatives to confirm the diagnosis of epilepsy using the ILAE (International League Against Epilepsy) guidelines. Skin biopsies were done for parasitological evidence of OV infestation.

**Results**

Food insecurity was evidenced in 51.5% of households. Stunted growth was found in 59.5 % (95%CI: 54.3-64.5) in children aged 5 – 18 years of whom 31.2 % (95% CI: 18.7 - 47-2) were severely affected (height-for-age index < 3 Z-score). Higher rates of stunting (up to 67%) were seen between 8 and 16 years of age. The mean (± SD) age for the onset of epilepsy was 13.2 (± 4.8) years. Familial history of epilepsy was reported in 69/84 cases (82.1%) with 14 subjects (16.7%) having at least 2 first-degree relatives with epilepsy and 26 subjects (31.0%) with up to 4 relatives in the extended family suffering from epilepsy. Most subjects i.e. 61/84 (72.6%) reported generalized tonico-clonic seizures with head nodding preceding the generalization of seizures in 3/84 cases (3.6%). On site examination of skin biopsies showed evidence of OV infestation.

**Conclusion**

Our findings suggest that nutritional deficiencies may play a role in the pathogenesis of epileptic syndromes observed in OV endemic areas. Further studies are needed to determine whether the transgenerational pattern may be explained by nutritional challenges or genetic polymorphisms, or their combination.

**Key-words:** Familial history of epilepsy, Food insecurity, Kasangulu Health District, Nodding syndrome, Stunting**.**

**Principal Investigators:** van der Kouwe, Andre

**Title:** Longitudinal Neuroimaging and Cognitive Study of HIV-infected children

**Presenters:** Ernesta Meintjes (University of Cape Town, South Africa), Andre van der Kouwe (Massachusetts General Hospital, Boston, USA), Barbara Laughton (Stellenbosch University, South Africa)

The developing brain is especially vulnerable to HIV due to rapid and critical brain development in the first 2 years of life. Pediatric HIV and ART-associated damage has been primarily investigated from neuropsychological and clinical perspectives. Few neuroimaging studies have assessed HIV-infected subjects stable on ART, particularly among young children, and none in developing countries. This longitudinal study involves neurocognitive and neuroimaging assessment at 5, 7 and 9 years in a subset of children from the randomized CHER (Children with HIV Early antiretroviral therapy) trial. Notably, these children all received standard government-regulated ART before 18 months of age, and in 90% viral loads were suppressed at the time of their first scan. HIV-infected children demonstrate white matter reductions and regional gray matter enlargements at 5 years, as well as regional reductions in gyrification, white matter integrity and functional connectivity at 7 years. We observed differences in all imaging measures between children who initiated ART before and after 12 weeks of age. Notably, immunocompromise at time of enrollment (7weeks) was associated with reduced neuronal integrity in the basal ganglia at age 5 years, irrespective of when ART was initiated. These findings

demonstrate long-term effects of HIV and/or ART, despite viral suppression. Further investigations are needed to establish whether differences persist throughout development.

**Principal Investigator:** Vaisberg, Abraham

**Title:** Drug Discovery for Mental Disorders: Preclinical Studies of Peruvian Botanicals

**Presenter:** Carla Gallo

Mental disorders are multidimensional and severely disabling diseases, with a strong need for pharmacotherapies with better adherence, long-term outcome and patient functionality. Unfortunately, the scientific advancements in the field have not yet led to the introduction of truly novel pharmacological approaches to treatment. One of the possible avenues to achieve this goal is to take advantage of world´s ancient knowledge of healing practices to direct search of new lead compounds, with expectedly novel action mechanisms that would lead to better treatment outcomes.

This R21 is part of a long range effort directed to the discovery of new pharmaceuticals from Peruvian flora traditionally used for the treatment of mental disorders. Previous studies have led us to collect information on the traditional use of plants for the treatment of mental disorders in several Peruvian localities and geographical regions. We currently have extracts from 477 plant collections corresponding to 265 species from 87 different plant families. These plants are traditionally used for one or more of the following activities: antipsychotic, antidepressant, anxiolytic and sedative. Importantly, about 60% of those species have never been described in the scientific literature for their potential effects on the modulation of behavior. Half of our plant extracts have been screened so far (partly with the support of this R21) to validate their traditional medical use with behavioral tests in mice. To date we have identified 157 plant extracts having one or more potential psychotropic activity (123 antipsychotic/antimanic, 84 anxiolytic and 38 antidepressant). Additionally, with this R21, our 477 extracts have been tested for 56 receptor targets in the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill (UNC), showing they are potentially active towards several targets of interest (e.g. serotonin 5-HT6 and 5-HT7A antagonists, nocioceptin/orphanin agonists, GPR68 antagonists, among others). This screening needs to be replicated for confirmation at the PDSP before proceeding further towards the isolation and identification of the active compounds. The availability of the whole set of PDSP activities for each extract is unique and opens up a cascade of opportunities for approaching drug discovery. A multidisciplinary network of US experts has been established and consolidated during this R21, with the aim to act as future R01 collaborators. Our new ongoing proposals are based on the following hypotheses: 1) it is possible to isolate bioactive principles from these plants; 2) animal behavioral models, molecular targets and reported use in traditional medicine are valid tools for screening/validation and for further prioritization of research; 3) analyzing the latter 3 tools in combination can potentiate the efficiency for identifying potential leads; 4) molecular target information will help to further understand the traditional medicine conceptualization of mental disorders in Peru as well as the construct validity of the animal behavioral models; 5) the isolated lead compounds –since they come from extracts of plants that are currently being used by humans- will be superior to those obtained from chemical libraries in terms of better bioavailability and less secondary effects. We are aiming to devise an experimental pipeline with a strategic planning/decision-making approach that will allow discovery with the best cost/benefit ratio. Within this aim we expect to confirm the activity of the extracts screened previously at the PDSP; to prioritize the bioassay-guided fractionation of the most appealing extracts; to develop or test new methods for the screening and bioassay-guided fractionation in order to identify novel psychotropic agents and avoid toxicity; to dereplicate and determine the molecular structure of the isolated active principle(s).